# 1 Simulated Data Analysis Example

```r
rm(list = ls())
require(survival)
# Installation of nphsim package install.packages('devtools')
# library(devtools) install_github('keaven/nphsim')
library("nphsim")
# Analyisis code
source("../R/cox_rhogamma_functions.R")
source("../R/km_resampling_functions.R")
source("../R/weighted_logrank.R")
```

```r
eta <- round(0.003991994, 3)
# Baseline hazard function
lam0 <- round(0.07675284, 3)
# change-point(s) at 6-months HR=1 for t<6; HR=0.5 for t>=6
intervals <- c(6)
hr.cp <- c(1, 0.5)
lambdaC <- c(lam0, lam0)
lambdaE <- hr.cp * lambdaC
n <- 150
EDr <- 0.7
## e.g., EDr=0.70 --> 70% of sample size
event.trigger <- round(EDr * (2 * n))
R <- c(3, 3, 6)  # enrollment period: total of 12 months.
gamma <- c(2 * c(n/6, n/3, n/2)) * c(1/3, 1/3, 1/6)  # ramp-up enrollment
set.seed(8316951)  # Initialize seed for simulated dataset
# Single simulated dataset
sims.data <- nphsim(nsim = 1, lambdaC = lambdaC, lambdaE = lambdaE, intervals = intervals,
    ssC = n, ssE = n, gamma = gamma, R = R, eta = eta)
# Extract data corresponding to analysis datacut
sims.cut <- simtest(sims.data, anatype = "event", anaD = c(event.trigger))
data.cuts <- sims.cut$simd
# ss<-1 (Extract the single simulated dataset)
ss <- 1
sim.data.s <- data.cuts[which(data.cuts$sim == ss), ]
# Simulated survival time
Y <- sim.data.s$aval
# Delta is event indicator (1=event; 0=censored)
Delta <- 1 - sim.data.s$cnsr
# Treatment indicator
X <- ifelse(sim.data.s$treatment == "control", 0, 1)
# Number of resamples=draws (synthetic martingale resampling)
draws <- 10000
set.seed(123)  # Initialize seed for resampling
# rgs=(rho,gamma): (0,0) denotes rho=0, gamma=0 (log-rank) (0,1) denotes
# rho=0, gamma=1 (etc) (-1,-1) includes RMST
rgs <- list(c(0, 0), c(0, 1), c(1, 0), c(1, 1), c(-1, -1))

temp <- fit.combo.wlr(rgs = rgs, time = Y, delta = Delta, z = X, draws = draws,
    plot.rg = TRUE, print.results = FALSE)
```
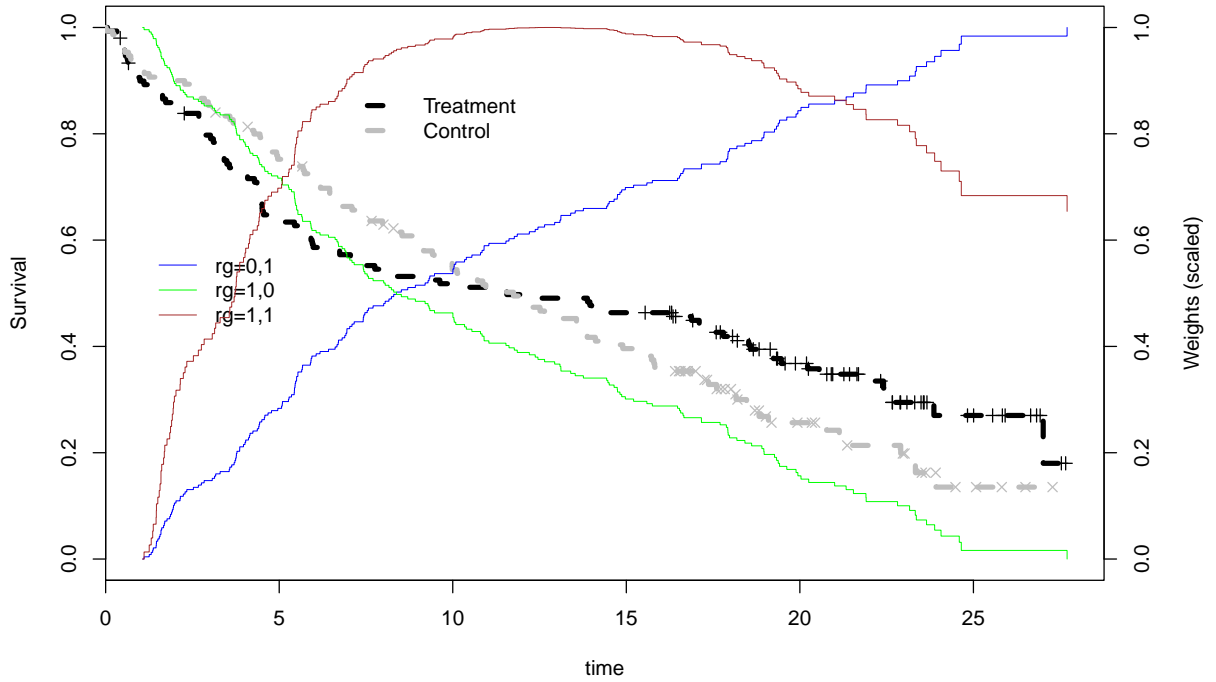
```r
est.out <- temp$WLR
rs <- est.out$rho
gs <- est.out$gamma
# Extract RMST
rmst <- est.out[which(rs == -1 & gs == -1), ]
wlr.est <- as.data.frame(est.out[which(rs >= 0), c("est", "se.est", "Z.score",
    "pval(Z)", "estL", "estU", "estL.sb", "estU.sb")])
rownames(wlr.est) <- c("Cox", "FH(0,1)", "FH(1,0)", "FH(1,1)")
colnames(wlr.est) <- c("HR", "SE", "Z", "pvalue", "Lower", "Upper", "Lower",
    "Upper")
# Max combo test and companion estimate
maxcox <- temp$CoxMax
```

```r
options(digits = 5)
library(knitr)
library(kableExtra)
options(knitr.table.format = "latex")
kable(wlr.est, format = "latex", booktabs = TRUE, digits = c(3, 3, 3, 5, 4,
    4, 4, 4), longtable = FALSE, caption = "\\label{tab:simanalysis} Simulated data analysis") %>%
    kable_styling(full_width = FALSE, latex_options = c("scale_down")) %>% add_header_above(c(` ` = 5,
    `Pointwise 95% CI` = 2, `Simultaneous 95% CI` = 2))
```

Table 1 displays the $\rho\gamma$-weighted Cox models corresponding to the Zmax4 test. The Zmax4 test (adjusted) p-value is 0.006 with companion Cox model estimated hazard ratio of = 0.639 (95% CI= 0.4401, 0.9264). The RMST estimate is 0.784 (95% simultaneous CI= -1.807, 3.375) with p-value=0.248. Note that the total minutes for resampling (draws=10^4) is 2.76017.

Table 1: Simulated data analysis

	HR	SE	Z	pvalue	Pointwise 95% CI Lower	Upper	Simultaneous 95% CI Lower	Upper
Cox	0.852	0.119	1.155	0.12409	0.6480	1.1189	0.6220	1.1657
FH(0,1)	0.639	0.105	2.767	0.00283	0.4620	0.8825	0.4401	0.9264
FH(1,0)	0.997	0.146	0.020	0.49183	0.7483	1.3283	0.7168	1.3867
FH(1,1)	0.726	0.109	2.135	0.01638	0.5410	0.9755	0.5176	1.0196

In the following we compare to the asymptotic approach as implemented in the nphsim package function rm.combo.WLRmax (See https://rdrr.io/github/keaven/nphsim/man/rm.combo.WLRmax.html).

Note that the above approach is applicable to combining weighted log-rank tests which does not include RMST.

```r
# Remove RMST for comparison with asymptotic
rgs <- list(c(0, 0), c(0, 1), c(1, 0), c(1, 1))
set.seed(123)   # Initialize seed for resampling
temp <- fit.combo.wlr(rgs = rgs, time = Y, delta = Delta, z = X, draws = draws,
    plot.rg = FALSE, print.results = FALSE)
est.out <- temp$WLR
rs <- est.out$rho
gs <- est.out$gamma
# Extract RMST
wlr.est <- as.data.frame(est.out[which(rs >= 0), c("est", "se.est", "Z.score",
    "pval(Z)", "estL", "estU", "estL.sb", "estU.sb")])
rownames(wlr.est) <- c("Cox", "FH(0,1)", "FH(1,0)", "FH(1,1)")
colnames(wlr.est) <- c("HR", "SE", "Z", "pvalue", "Lower", "Upper", "Lower",
    "Upper")
# Max combo test and companion estimate
maxcox <- temp$CoxMax

# Compare with nphsim function rm.combo.WLRmax which calculates combination
# tests based on asymptotics
library(dplyr)
library(Matrix)
temp2 <- rm.combo.WLRmax(time = Y, status = Delta, arm = X, wt = list(a1 = c(0,
    1), a2 = c(1, 0), a3 = c(1, 1)), adjust.methods = "asymp", one.sided = TRUE)
```

```r
options(digits = 6)
library(knitr)
library(kableExtra)
options(knitr.table.format = "latex")
kable(wlr.est, format = "latex", booktabs = TRUE, digits = c(3, 3, 3, 5, 4,
    4, 4, 4), longtable = FALSE, caption = "\\label{tab:simanalysis2} Simulated data analysis") %>%
    kable_styling(full_width = FALSE, latex_options = c("scale_down")) %>% add_header_above(c(` ` = 5,
    `Pointwise 95% CI` = 2, `Simultaneous 95% CI` = 2))
```

Table 2 displays the $\rho\gamma$-weighted Cox models. The combination test (adjusted, 1-sided) p-value is 0.006 with companion Cox model estimated hazard ratio of $= 0.639$ (95% CI$= 0.4409, 0.9248$). Note that the total minutes for resampling (draws$=10^4$) is 2.495333. The asymptotic p-value and Cox estimate via rm.combo.WLRmax() function is 0.006874 and 0.638512 with CI$= 0.442318, 0.921728$.

Table 2: Simulated data analysis

	HR	SE	Z	pvalue	Pointwise 95% CI		Simultaneous 95% CI	
					Lower	Upper	Lower	Upper
Cox	0.852	0.119	1.155	0.12409	0.6480	1.1189	0.6230	1.1640
FH(0,1)	0.639	0.105	2.767	0.00283	0.4620	0.8825	0.4409	0.9248
FH(1,0)	0.997	0.146	0.020	0.49183	0.7483	1.3283	0.7179	1.3845
FH(1,1)	0.726	0.109	2.135	0.01638	0.5410	0.9755	0.5184	1.0180